Can we increase adolescent growth?

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Abstract

Adolescent growth represents 15–20% of adult height and has been the focus of several treatment interventions, aiming at increasing the amplitude of the adolescent spurt. Importantly, pre- and early puberty are times when patients and families seek medical help and when estimates of adult height are more accurate than in younger children. We review the current approaches aimed at increasing pubertal growth in short children and knowledge about their results and risks. GnRH agonists, when used outside the context of precocious puberty, induce a modest gain (4 cm) when they are used for more than 3 years. Their effects on bone mass, body composition and possibly on psychosocial parameters limit their use. Several trials have now shown that GH can increase adult height of short adolescents with idiopathic short stature or born small for gestational age. However, the amplitude of the effect is modest and of dubious clinical significance. Lastly, the association of both approaches is rather popular among pediatric endocrinologists but still lacks a definite demonstration of its efficacy. In conclusion, we have gained insight in the median effects of some of these treatments and overoptimistic initial expectations are now refocused. However, we still have a long way to go before we truly evaluate the factors affecting the variable individual responses to these treatments, their clinical significance and their cost–benefit balance.

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Introduction

Pubertal growth represents 15–20% of adult height and has been the focus of several treatment interventions, aiming at increasing the amplitude of the pubertal spurt. Importantly, pre- and early puberty are times when patients and families seek medical help to evaluate height prognosis and ultimately try to increase adult height if they see the estimate as unfavorable. In addition, at this time in life, adult height prognoses are more accurate than in younger children, allowing targeting of medical intervention on the right individuals. Here we will review current approaches aimed at increasing pubertal growth and knowledge about their results and risks.

Normal pubertal growth

Pubertal growth represents approximately 15–20% of adult height and precedes the fusion of growth plates. Before puberty, growth does not proceed at a constant rate as generally thought, but declines progressively with age. This explains why growth velocity can be 'physiologically' low in delayed puberty and why the inflexion point can be missed if puberty occurs very early, since 'prepubertal' growth can be rather rapid.

As examples, the 95% confidence interval (CI) of growth velocity in prepubertal girls is 5.1 to 9.3 cm/year at 4 years and 3.9 to 7.3 cm/year at 8 years. After the prepubertal decline, growth velocity increases and reaches a peak, on average 22 months later, and declines (1). The total amplitude of the pubertal spurt (from the inflexion point to adult height) is not a fixed value and varies negatively with the age of onset of puberty (1, 2). Similarly to the amplitude of the growth spurt, peak growth velocity, one of its components, decreases with age at pubertal onset (1–3). Therefore a compensatory mechanism occurs where individuals with earlier puberty grow less before puberty and more during puberty while those with late pubertal development start their puberty taller but grow less during puberty. Whether this compensation is complete and whether those who enter puberty at the earlier end of the normal spectrum end up shorter than those who mature later is still a matter of debate (4). Normal Spanish boys who entered puberty (G2 stage) at mean ages of 11, 13 or 15 years reached similar mean adult heights (5). In contrast, a study (3) performed in a large series of American girls indicated a higher adult height in girls with late (> 12.9 years) vs early (< 11.7 years) age at menarche. The median difference was 2.6 and 1.7 cm in white and black girls respectively. Interestingly, in childhood and

early adolescence, early maturers were taller, had higher body mass index (BMI) and thicker skinfolds than later maturers. This points to the tight interactions between fat mass and pubertal development. The other variables affecting the pubertal growth spurt have not been recognized so far, but it is likely that characteristics of the growth plate will be identified.

Another important point to consider is the concordance between the growth spurt and clinical pubertal development (1, 6, 7). Most investigators use clinical pubertal development as landmarks for pubertal growth, hindering this analysis. However, when using auxological parameters to identify the spurt, it is possible to evaluate its concordance with clinical Tanner stages. In girls, the acceleration of growth generally occurs before or during the first year of breast development. In boys, the acceleration of growth occurs later, in general during the second year of pubertal development. There are of course large individual variations around this median pattern. In girls, peak growth velocity occurs at stage B2 in 40% of individuals, B3 in 30%, B4 in 20% and B1 (before breast development) in 10% (1). Similarly, in boys, peak growth velocity occurs at stage G3 in 60% of individuals, G4 in 28%, G2 in 8% and G5 in 4% (1). The mechanistic basis of these variations is essentially unknown. However, current concepts on the respective roles of estradiol and testosterone on the growth plate explain the different tempo of pubertal growth in boys and girls (8). Observations made in patients with androgen or estrogen resistance or with aromatase deficiency indicate clearly that in both sexes estradiol is the active hormone involved in bone metabolism and growth plate maturation. The sexual dimorphism in the tempo of pubertal growth is likely to be due to the delay needed for estradiol level to reach a certain threshold after aromatization from testosterone in boys (8).

Another important component of pubertal growth relates to the amount of body fat. The acceleration of growth and puberty associated with common obesity is well known and some of the variations of pubertal components are probably related to the progressive increase in body fat in the population. The influence of childhood adiposity on pubertal growth has been analyzed in a longitudinal study of normal children (9). The evolution of height in standard deviation between the age of 8 and adult height was taken as a (relative) measure of the adolescent growth spurt and was related to the evolution of BMI between the ages of 2 and 8. The findings indicate that an additional gain of 1 BMI point (+1 kg) decreases the adolescent growth spurt by a mean of 0.5 cm in girls and 0.9 cm in boys. The 'reduced' adult height in girls with early vs late maturation discussed above (3) probably relates to a similar mechanism. The aromatization of androgens of adrenal or gonadal origin by the adipose tissue is probably involved.

Other non-endocrine factors certainly affect the kinetics of growth plate maturation around the age of puberty. Although their role in normal physiology is not known, two pathological examples highlight their importance. FGFR3, one of the fibroblast growth factor receptors, is expressed in the growth plate and is involved in several constitutional bone disorders leading to short stature, including achondroplasia and hypochondroplasia (10–12). In these disorders, activating mutations of the receptor lead to premature closure of the epiphyses and to short stature. Conversely, in a mouse model, targeted disruption of the receptor leads to tall stature, indicating an influence of FGFR3 on the regulation of growth plate physiology (13). Pseudohypoparathyroidism is another pathological example where premature closure of the growth plate occurs in the absence of a sex-steroid signal. In this disease, loss of function mutations of GNAS1, the gene encoding for the alpha-subunit of the regulatory Gs protein, leads to resistance to parathyroid hormone and other hormones (14–16). In addition, 'ectopic' bone formation leads to subcutaneous calcifications and accelerated growth plate fusion, leading to the well-known metacarpal shortness and to the lack of pubertal growth spurt in these patients. Similar but more subtle variations in growth plate function might contribute to the adolescent growth spurt and have recently been reviewed (17).

The short child at onset of puberty

Although it is obvious that short stature should be evaluated as early as possible, many short stature patients present around pubertal ages, after the age of 9 in girls and 11 in boys. These patients need a complete workup that is beyond the scope of this review and it is not rare to identify at this stage acquired conditions such as craniopharyngioma, inflammatory bowel diseases, celiac disease or constitutive conditions such as Turner's syndrome, skeletal disorders (short stature homeobox (SHOX) gene defects, hypochondroplasia etc.). However, in most cases, a diagnosis of idiopathic short stature or constitutional delay of growth and puberty is made, opening the question of the adult height prognosis and its adequacy with the familial target height and with the individual's wishes.

In such cases, the Bayley–Pinneau method is the most popular one to evaluate the growth prognosis. We have been able to evaluate the accuracy of the method in a series of 63 children, who were seen around the age of 11 and were followed to adult height (Table 1). There is a trend for overprediction in boys and underprediction in girls and in both cases a very wide inter-quartile range (6 cm in boys, 8 cm in girls). Although the method looks rather satisfactory overall in clinical studies, the accuracy of prediction is very insufficient for individual cases. In addition, identifying the cause of the short stature or limited adult

Table 1 Difference between predicted and actual adult height (cm) in untreated children evaluated around the age of puberty.

	<i>n</i>	Median	1st quartile	3rd quartile	Min	Max
Boys	32	−1.3	−4.0	+2.0	−19	5
Girls	31	+1.2	−1.9	+6.0	−10	9

height prognosis should be a priority, since it will impact on the precision of the prognosis; as an example a short prepubertal girl with Turner syndrome will have a far worse growth prognosis than a girl with similar auxological characteristics and constitutional short stature.

Although in most cases, regular follow-up and reassurance are the best options, several therapeutic approaches have been discussed in short patients at the onset of puberty. It is clear that at this point many of these treatment options have not been fully validated and should not be considered as a standard of care unless they have been approved for use by regulatory authorities in a given country.

Gonadotropin-releasing hormone (GnRH) agonists in short children at onset of puberty

The depot forms of GnRH agonists efficiently suppress the gonadotropic axis and the introduction of 3-month depot forms has made their use even easier than with the traditional 1-month depot forms (18). In precocious puberty, the median height gain measured by the Bayley–Pinneau method ranges from 3 to 10 cm in recent studies (19), with several factors affecting height outcome. The results observed in precocious puberty and the hope that interrupting puberty might increase adult height has led to several attempts to use GnRH agonists in patients other than those with strict criteria for precocious puberty, in particular children with normal puberty and poor growth prognosis due to idiopathic short stature.

Only a few studies have presented adult height data after treatment with GnRH agonists alone (Fig. 1). In our study, 31 girls with idiopathic short stature and pubertal onset around the age of 12 were treated for an average of 1.9 years. The results were disappointing since the increase of adult over pretreatment-predicted height was 1 ± 2.3 cm ($P < 0.02$) (20). More importantly, growth velocity markedly declined during treatment and the height deficit increased by 0.4 SDS on average in these already short girls. Although no psychological outcome was evaluated in our study, treatment was poorly perceived by many of the girls. In the recent and long awaited NIH study, the same issue was addressed through a placebo-controlled randomized study (21). The population was quite heterogeneous, with half of the patients diagnosed as having idiopathic short stature and the other half having various conditions affecting

Figure 1 Evolution of height prognosis during treatment with a GnRH agonist in children with short stature. (A) Mean treatment duration = 3.5 years, $n = 25$ (LH-RH agonist) and 22 (placebo); $*P < 0.05$, $\dagger P < 0.01$; means $\pm$ s.d. are shown. Adapted from (21), with permission from the Massachusetts Medical Society, copyright 2003; (B) mean treatment duration = 1.9 years, $n = 31$, mean $\pm$ s.d. are shown. Adapted from (20), with permission from The Endocrine Society, copyright 1996. LHRH, luteinizing hormone-releasing hormone.

growth, ranging from Cushing's disease to bone disorders. One third of the adolescents were also treated with growth hormone (GH). The mean duration of treatment was 3.5 years and treatment was stopped around the age of 15.5 years in girls and 17 years in boys. Covariance analysis of adult height SDS, adjusted on sex, GH treatment, baseline height SDS, target and predicted height SDS showed an increase of 0.6 SDS (95% CI 0.2 to 0.9 SDS) with the use of GnRH agonist. Translated into centimeters, the difference was 4.2 cm (95% CI 1.7 to 6.7 cm). There was no difference according to sex, although the results suggested a better effect in boys. The treatment was associated with a decrease in bone mineral density, measured 1 year after the discontinuation of the treatment.

Although one might view these results as discrepant, they are indeed very consistent and indicate that GnRH agonists have two effects, reducing the growth rate and the bone age progression, resulting in opposite effects on adult height. When these treatments are used for short periods of time (as in our study), the effect on adult height is close to zero since these two factors

counterbalance each other. However, when duration of treatment increases, the slow growth rate observed in the absence of bone age progression eventually converts into increased adult height, roughly 1 cm per treatment year. In addition, other studies in children with 'premature' or 'early' puberty and decreased predicted height have made similar observations, i.e. that short treatments with GnRH agonists led to no or clinically insignificant adult height gains (19, 22, 23). This is reminiscent of the increased adult height of patients with hypogonadism, only if untreated to the age of 20 years (24). Similarly, in males with estrogen receptor or aromatase deficiency, height is normal or low around the age of puberty in the absence of a growth spurt. However, persistent growth in the absence of growth plate fusion leads to tall stature when patients are older than 20 years (8, 25, 26). The identification of non-endocrine factors involved in growth plate maturation will certainly increase our understanding of the relative importance of endocrine and non-endocrine factors.

In sum the data accumulated so far allow the clinician to give in-depth explanations to patients and families: short treatments are completely ineffective and long treatments have some efficacy with questionable clinical significance (4 cm) and serious safety concerns. In addition, the psychological sequelae of drug-induced severe pubertal delay have to be evaluated. Therefore, GnRH agonist treatments to increase height outside of precocious puberty are not currently advised outside research protocols (21, 27).

GH in short children at onset of puberty

GH is increasingly used in short children and is now approved in Europe for use in short children born small for gestational age. However, this indication covers a wide range of clinical situations and does not exclude the treatment of these short children when first seen around the age of puberty. We have obtained data relevant to this topic in two situations. First in analyzing a large cohort of children treated in France for idiopathic GH deficiency and secondly in a clinical trial aiming at improving adult height in children born small for gestational age.

In the first situation (28), we tried, by analyzing a population-based series of patients treated for GH deficiency, to evaluate the effect of GH on adult height. It could be viewed as paradoxical to use children with GH deficiency when elaborating on the effect of GH in idiopathic short stature. However, the mean age at onset of treatment (12.6 years) and the fact that more than 90% of the children had stimulated GH peaks over 5 ng/ml classifies them more accurately in the idiopathic short stature group than in the true GH-deficient group (29, 30). As shown in Fig. 2, we classified patients between those who had completed their treatment until the near-end of growth (roughly 50% of the 2852

Figure 2 Height outcome in short children treated with GH for GH deficiency: results of the France-Hypophyse database; reprinted from (28).

patients followed to adult height) and those who had stopped treatment at various time points before reaching this stage. In the direct analysis of data, all groups gained about 1.1 SDS, raising the question whether this was due to spontaneous catch-up in individuals with delayed puberty or to the effect of GH. In particular, patients who had used GH for the shortest period of time (less than 18 months) did similarly to those who used treatment for the longest periods. In multivariate analysis we tried to take into account several factors associated with growth, resulting in a model explaining 58% of the variance of height gain expressed in SDS. Most of the factors identified were unrelated to the treatment and only 4% of variance was explained by treatment variables. Quite interestingly, completion and duration of the treatment had opposite effects, with children with 'incomplete' treatments gaining more and longer treatments associated with higher gains (28). The mean effect was close to 1 cm of adult height gain by year of treatment. Other than the limits of a multicenter observational study, the two caveats of our study are first the relative heterogeneity of the patients who were mostly selected by their height and their (unreliable) response to GH provocative stimuli (31) and the

relatively low dose of GH used (0.4 U/kg per week or 0.02 mg/kg per week).

In a completely different context, we evaluated the effect of relatively high doses of GH (1.4 U/kg per week or 0.067 mg/kg per day) in short adolescents born small for gestational age (32). The strengths of this study were to include a randomized untreated control group and that more than ~90% of patients in the treated group were followed to adult height. Quite interestingly the initial features (other than the GH stimulation tests) were very similar to those of the GH-deficient children of the France–Hypophyse database. Here we could conclude that treatment had induced a height gain of 0.6 SDS with a 95% CI of 0.27 to 0.89 SDS, with an average duration of treatment of 2.7 years (Table 2, Fig. 3). The only independent variable associated with outcome (other than treatment itself) was bone age delay, confirming the validity of its use to predict adult height in short adolescents. Interestingly, the estimate of the effect (0.6 SDS in 2.7 years or 0.2 SDS/year) is of the same order of magnitude as in the France–Hypophyse database, although the dose varies by 3-fold between the two studies, raising the question of the dose relationship.

Table 2 Adult height (cm) in short adolescents born small for gestational age in a randomized GH or control study; adapted from (32), with permission from The Endocrine Society, copyright 2003. Values are means $\pm$ s.d.

	Controls <i>n</i> = 33	GH-treated <i>n</i> = 91
Boys	159 $\pm$ 5	162 $\pm$ 7
Girls	147 $\pm$ 5	151 $\pm$ 5

Other studies have addressed similar questions and have obtained quite similar results (33, 34). Altogether, these results demonstrate that GH given alone can increase the pubertal growth spurt in short adolescents. Similar to our conclusions with GnRH agonists, the physician now has precise information to give to patients and families on what to expect from a GH treatment in such a situation. She or he can discuss the clinical significance of such height gains, given the fact that all attempts to demonstrate benefits of such height gains on psychosocial parameters have so far failed (35). She or he can also discuss the constraints and risks of such treatments and the uncertainties concerning long-term consequences (36–39). Also to be taken into account, but probably to be left to regulatory authorities, is the cost–benefit ratio of those approaches, and for instance, in our randomized study, the average current cost of treatment was estimated to be 100 000€ (37 000€ per year).

Combination of GH and GnRH agonists in short adolescents

The possibility to block pubertal development and skeletal maturation as a tool to increase the effect of GH treatment has long been considered. However, to date, we only have hints on the true efficacy of the combination, while the definitive trial evaluating this approach is still lacking. Hence, as mentioned above, the relative ease of use of GnRH agonists has made them a popular additive to GH treatments given within approved indications. For instance when looking at large databases of GH-treated children, the number also receiving GnRH agonists is rather significant: 249

Figure 3 Height outcome in short adolescents born small for gestational age in a randomized GH or control study; boys and girls are represented by squares and circles respectively; reprinted from (32), with permission from The Endocrine Society, copyright 2003.

of 21 641 (1%) in the KIGS database (40), 509 of 16 000 (3%) in the NCGS database (41), and in the France-Hypophyse database of 2852 children, 7% of boys and 11% of girls (28). It is noteworthy that since our study focused on patients having attained adult height, it selected older patients, artificially raising the proportion of those who had received GnRH agonists. The question of the efficacy of the combination is hard to address in observational databases. The KIGS study (40), by comparing the 39 of the 249 combination patients who were followed to near-adult height with 1893 treated with GH alone, observed a lower total height gain (from start of GH treatment to adult) in the combination patients than with GH alone (-0.3 SDS in girls and -0.5 SDS in boys). We made a similar observation and, in multivariate analysis, use of GnRH agonist was associated with a 0.3 SDS decrease in adult height gain (28). However, looking further at the data, it became obvious that patients treated with the combination had poorer growth prognosis than those treated with GH alone. When introducing age at onset of puberty in the multivariate analysis, the influence of GnRH agonists disappeared, suggesting that the indication, not the treatment, was the cause for the decreased growth in those receiving the GH + GnRH agonist combination. Other smaller studies have addressed the same question (GH + GnRH agonist combination in GH deficiency), using patients selected from local or national databases or from small-scale trials (range 7–23 combination patients per study) (42–45). The mean durations of the combination was quite variable ranging from 1.4 to 3 years. Most studies concluded at a benefit from the combination ranging from 0.8 to 1.4 SDS (42–44). In one study there was no benefit for the entire group of patients, but subset analysis suggested some effect in patients born small

for gestational age (45). Altogether, we can derive no firm conclusion from these observational databases or small-scale studies, but observe that a high number of patients are so treated outside of the approved indication of GnRH agonists in children (precocious puberty).

Obviously the use of the combination of GH and GnRH agonists is a major focus of interest in children with normal endocrine status, with a diagnosis of idiopathic short stature or born small for gestational age. Although several studies have been produced showing variable effects, few of them have included a relevant control group (Fig. 4). Pasquino *et al.* (46) have compared 12 short normal girls treated with the combination vs 12 treated with GH alone. At adult height, the gain over predicted height was 10 ± 2.9 cm with the combination vs 6.1 ± 4.4 cm with GH alone, i.e. a mean difference of 4 cm. In the Dutch study, 36 patients were randomized to combination treatment or observation (47). Although the final results have not been presented yet, predicted height at the end of the 3-year treatment period was higher by a mean of 1.2 SDS in the treated vs control group. These studies are encouraging but real adult height data have to be analyzed to really measure the effect of the combination treatment in short adolescents. Of course, in addition to the effectiveness of the approach in terms of centimeters, tolerance issues have to be addressed (does GH prevent GnRH agonist-induced loss of bone mass, etc?). The issues of clinical significance and cost effectiveness are the same as discussed above.

Other approaches to increase adolescent growth

Although GH and/or GnRH agonists have been the major focus of clinical research on pubertal growth in

Figure 4 Height outcome in short adolescents treated with the combination of GH and GnRH agonists in a selected study. (A) Predicted adult height (PAH) during treatment in the Dutch randomized control study; GH + GnRH, $n = 18$; controls, $n = 16$; $**P < 0.05$; $@P < 0.001$; means $\pm$ S.E.M. are shown. Adapted from Kamp *et al.* (47), with permission from The Endocrine Society, copyright 2001; (B) outcome in the study by Pasquino *et al.* (46); $n = 12$ per group; mean $\pm$ S.D. are shown. Adapted from (46), with permission from The Endocrine Society, copyright 2000.

the past decade, other approaches have been proposed. Sex steroids are commonly used, in particular testosterone in boys, to hasten sexual maturation and increase growth in constitutional pubertal delay. Although these treatments are generally considered not to affect adult height, they meet the needs of most of the children seen for short stature at entry of puberty, i.e. correct their transient height deficit compared with their peers with normally timed puberty. These treatments are considered safe and are remarkably cheap in comparison with those discussed above (48). Their use has been discussed in several reviews (49, 50).

More recently, the use of aromatase inhibitors has been proposed to specifically decrease the growth-maturing effects of estrogens on the growth plate and therefore increase adult height (51). So far, these treatments have only been used in pediatric endocrinology in rare patients with gonadotropin-independent precocious puberty (52, 53). This approach has recently been reviewed elsewhere (54) and awaits further efficacy and safety data.

Conclusion

Although the current state of the art could look rather disappointing, with many questions remaining unanswered, we have gained insight into the median effects of some of these treatments and overoptimistic initial expectations are now refocused. However, we still have a long way to go before we truly evaluate the factors affecting the variable responses to these treatments, their clinical significance and their cost-benefit balance.

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